- Second Declaration of Dr. John Altman under 37 C.F.R. § 1.132, with attachments.

REMARKS

Status of the Claims

Claims 19 - 55 and 61 - 63 are pending. Pursuant to election of species, claims 22, 34 - 38, 41, 42, 44, 46, and 48 have been withdrawn, to be rejoined upon allowance of a claim generic thereto, 37 C.F.R. § 1.146. Claims 19 - 21, 23 - 33, 39 - 40, 43, 45, 47, 49 - 55 and 61 - 63 have been examined.

Written Description Rejection

The Examiner rejects claims 19 - 21, 23 - 33, 40, 43, 45, 47, 49 - 55 and 61 - 63 under 35 U.S.C. § 112, first paragraph, on the ground that applicants' specification provides inadequate written description support for the genus embraced by the recited claim element "inhibitors of cytokine secretion".[1] Applicants respectfully traverse the rejection.

"A specification may, within the meaning of 35 U.S.C. §112 ¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses". *Utter v. Hiraga*, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988). It suffices that the specification "convey with reasonable clarity to those skilled in the art

[1] Claim 39, which explicitly recites a species of such secretion inhibitor, Brefeldin A, is free of the rejection.

that, as of the filing date sought, [the inventor] . . . was in possession of the invention." *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). *Accord, Fujikawa v. Wattanasin*, 39 USPQ2d 1895, 1904 (Fed. Cir. 1996) ("the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question").

Applicants respectfully commend the Examiner's attention to the Declaration of Calman Prussin, of record in this application, and particularly to paragraphs 6 - 19, in which Dr. Prussin describes the prior art use of either monensin or Brefeldin A in the flow cytometric measurement of intracellular cytokines, clearly suggesting that one skilled in the art would have viewed the two as interchangeable.

Applicants further here reiterate that applicants' specification would reasonably have conveyed to persons skilled in the art that the inventors were in possession of the methods as broadly claimed, the ordinarily skilled artisan readily recognizing monensin as the second of two species of secretion inhibitor equivalent in effect in the claimed methods.

Applicants respectfully request reconsideration and withdrawal of the Examiner's rejection.

Denial of Priority Claim

The Examiner denies priority to parent application no. 08/760,447, filed December 6, 1996 ("the '447 application"), on two of the three grounds first advanced in the office action mailed January 30, 2001 and on a third ground newly proffered in the present office action.

Applicants respectfully traverse the denial and request reconsideration thereof.

The first of the reiterated grounds for denial is based on the Examiner's earlier assertion that "the '447 application discloses and claims methods of assessing T cell***s*** within a population" whereas, "[i]n contrast, the instant application discloses and claims a method of detecting ***individual T cells*** that respond to a[] . . . nominal antigen."[2]

In response, applicants had argued that the Examiner had failed adequately to appreciate that

> each and every dot on the 35 dot plots presented in FIGS. 1 - 4 of the '447 application represents a single cell that has been individually queried by the flow cytometer's laser. When the '447 specification says that "48,000 events, gated on viable CD4+ lymphocytes, are shown in each plot,"[3] the "events" of which the specification speaks are individually queried and characterized $CD4^+$ T cells.[4,5]

The Examiner responds in the present office action by stating that "it is the Examiner's position that said figures do not display individual, discrete, dots

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[2] Office action of January 30, 2001, p. 5; first emphasis in the original, second emphasis added.

[3] '447 specification p. 5, lines 4- 5; p. 5, line 18; p. 6, line 6; p. 6, lines 22 - 23.

[4] The figures thus present data on 35 x 48,000 = 1,680,000 individual T lymphocytes.

[5] Amendment and response mailed July 30, 2001.

(presenting individual events), nor are they meant to."[6] But in truth they do, and indeed they are.

> **Dot plot**: A two parameter data graph used for acquisition and analysis. **Each dot on the display represents one event** that the flow cytometer analyzed. Also known as a cytogram or a dual parameter correlated plot.[7]
>
> **Dual Parameter Dot Plots**. When two parameters need to be correlated a dot plot or scattergram is obtained by plotting the **individual measurements for each cell** against each other, the two axes are usually represented by channel numbers as described for histograms or by a logarithmic scale if appropriate.[8]
>
> If we now want to go further and correlate one parameter with another, software analysis packages implement the drawing of two-dimensional plots. Each cell is placed on the plot according to its intensity channel for each of the selected two parameters. Six two-parameter correlations can be derived from our four-parameter data (Fig. 4.2; keep in mind that each two-parameter correlation could be plotted with the x and y axes reversed). Dot plots show, simply, a dot on the page or screen at each locus defining quantitatively (according to channel number) the two relevant characteristics **of each particle** in the sample.[9]

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[6] Office action mailed August 31, 2001, p. 3.

[7] Flow Cytometry Glossary, Applied Cytometry Systems, http://www.appliedcytometry.com/gloss.htm, downloaded 12/12/01 (exhibit 1).

[8] "An introduction to flow cytometry: dual parameter dot plots," http://www.uwcm.ac.uk:10080/study/medicine/haematology/cytonetuk/introcution_to_fcm/dot_plots.htm, downloaded 12/12/01 (exhibit 2).

[9] Givan, Flow Cytometry: First Principles, 2nd ed., Wiley-Liss, Inc., 2001 (ISBN:0-471-38224-8), p. 48 (attached

Dot plot: A dot plot is a two-dimensional diagram correlating the intensities of two flow cytometric parameters **for each particle**.[10]

Dot Plot: A two parameter data graph used for acquisition and analysis. **Each dot on the display represents one event** that he flow cytometer analyzed.[11]

dot plot. A WinMDI dot plot displays correlated data from any two listmode parameters at a 256 x 256 resolution **on an event by events basis**.[12]

The most common and useful forms of display are the frequency histogram and the dual parameter correlated plot, often known as a cytogram or dot plot. . . . The cytogram or dot plot is a two-dimensional extension of the frequency histogram. In this case, the locations in memory correspond to a two-dimensional array of the channels of one ADC correlated against the channels of a second. Each location within the array is incremented according to the digitized values produced by the two ADCs. The memory can then be read on to the screen to produce a square plot where **each cell is**

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hereto as exhibit 3) (emphasis added).

[10] Givan, Flow Cytometry: First Principles, 2nd ed., Wiley-Liss, Inc., 2001 (ISBN:0-471-38224-8), pp. 241 - 242 (attached hereto as exhibit 3).

[11] "General flow cytometry glossary and cell cycle analysis terminology", The Janis V. Giorgi Flow Cytometry Laboratory: A Jonsson Comprehensive Cancer Center and UCLA AIDS Institute Shared Flow Cytometry Resource, http://cyto.mednet.ucla.edu/flow.htm (downloaded 12/12/01) (exhibit 4).

[12] http://facs.scripps.edu/help/html/term90s4.htm, downloaded 12/12/01 (exhibit 5).

represented at the coordinates appropriate to the measured values.[13]

And this surely should come as no surprise: "[f]low cytometry is a technique for making rapid measurements on particles or cells as they flow in a fluid stream **one by one** through a sensing point. The important feature of flow cytometric analysis is that **measurements are made separately on each particle within the suspension in turn** and not just as average values for the whole population."[14]

The second reiterated ground for rejecting applicants' priority claim is based upon the Examiner's earlier argument that "[e]ven the critical parameter, the length of the assay, is unclear in the parent application. While one figure indicates a 6 hour assay, the preferred embodiment (page 3) discloses a 101.5 hour incubation."[15]

In response, applicants had challenged the Examiner's legal authority *sua sponte* to impute a "critical parameter" into applicants claims, and on the basis of such imputed limitation to deny applicants' priority claim. Applicants had also offered a factual rebuttal.

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[13] Ormerod (ed.), Flow Cytometry: A Practical Approach, 2nd ed., Practical Approach Series, IRL Press at Oxford University Press, 1994, reprinted 1996 (ISBN: 0199634610) (exhibit 6).

[14] "Introduction to the principles of flow cytometry," in Flow Cytometry: A Practical Approach, Ormerod (ed.), at page 1, first paragraph, first two sentences.

[15] Office Action mailed January 30, 2001, p. 5.

In the present office action, the Examiner offers no rebuttal to applicants' legal argument, focusing exclusively on applicants' factual assertions.

Yet the legal impediment to the Examiner's action remains: the duration of incubation, which is not a claimed feature of applicants' broadest claims, cannot be imputed as a "critical parameter" (January 2001 office action) or "key element" (August 2001 office action) of such claims absent language in applicants' own specification to that effect. *A fortiori*, such imputed limitations cannot serve as the basis for the denial of applicants' priority claim.

The PTO itself recognizes that a rejection under § 112, first paragraph, "based on the grounds that a disclosed critical limitation is missing from a claim **should be made only when** the language of **the specification makes it clear** that the limitation is critical for the invention to function as intended. Broad language in the disclosure, including the abstract, omitting an allegedly critical feature, tends to rebut the argument of criticality."[16]

Nowhere has the Examiner pointed to where applicants' specification "makes it clear that the limitation is critical". And further, applicants maintain that "[b]road language in the[ir] disclosure . . . omit[s] . . . [the] allegedly critical feature", rebutting the argument of criticality.

At most, the Examiner's concerns about the adequacy of disclosure in the '447 application as to time of incubation can speak only to the priority of claims 54 and 55, which recite such limitations. It was, accordingly, as

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[16] M.P.E.P. § 2164.08(c), 7th ed., Rev. 1, Feb. 2000 (emphasis added).

to these claims alone that applicants offered, and again herein offer, a factual rebuttal to the Examiner's concerns.

The '447 application clearly discloses antigen incubations of 6 - 24 hours (providing explicit written description and enabling support for present claims 54 and 55). Thus, "this invention provides an assay protocol using peripheral blood mononuclear cells . . . for the rapid (generally less than 24 hours, preferably less than 6 hours), highly efficient, Ag-specific activation of secretion-inhibited CD4+ . . . T cells. . . ."[17] To similar effect, see '447 specification p. 6, lines 2 - 5; p. 8, lines 22 - 23; p. 9, line 36 - p. 10, line 3; '447 application original claims 9 and 10.

It is of no moment that the '447 application appears additionally to describe longer incubations,[18] for the requirements of section 112, first paragraph, are amply well met by the portions of the '447 disclosure identified in the paragraph immediately above, and claims 54 and 55 are therefore entitled to a December 6, 1996 priority date.[19]

In a final, newly stated, ground for denying applicants' priority claim, the Examiner argues that

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[17] '447 specification, p. 2, lines 30 - 33.

[18] And that the Examiner finds unpersuasive applicants' comment that the "101.5 hr" incubation was intended, but for typographical error, and would have been so understood by the skilled artisan, to read "1 - 1.5 hr".

[19] Applicants would add that the specification is to be read by the skilled artisan in the light of his knowledge of the art. As to such art, the references presently and formerly relied upon by the Examiner in rejections under § 103 — *e.g.*, Picker *et al.*, *Blood* 86:1408 - 1419 (1995); Application Note 1 (BD Biosciences December 19, 1996); Maino *et al.*, FastImmune™ Assay System (BD Biosciences) — all speak to incubations of 4 - 24 hours.

"[a]pplicant had not envisaged the instant invention, including all the claimed limitations, such as the use of whole blood (instant Claim 1) instead of purified PBMC, at the time of filing of the '447 application."

Claim 1 is not presently pending. Among the claims presently pending, the "whole blood" limitation appears only in claim 26 and claims dependent therefrom. All other claims recite, either explicitly or by dependency, "sample containing peripheral blood mononuclear cells", which element is amply well supported by the '447 specification. See, *e.g.*, '447 specification p. 2, lines 30 - 32; p. 3, line 21; p. 5, lines 1 and 12; page 6, lines 2, 19 and 30; p. 8, lines 14 - 16 and 22 - 23; p. 9, lines 24 - 29; '447 claim 1 as filed.

Applicants thus traverse the denial of priority on this final ground as to all claims except claims 26 - 30,[20] and respectfully request reconsideration and withdrawal of the Examiner's rejection of the priority claim as to claims 19 - 21, 23 - 25, 31 - 33, 39 - 40, 43, 45, 47, 49 - 55, and 61 - 63 .

Rejections under 35 U.S.C. § 103

Claims 19 - 21, 23 - 33, 39 - 40, 43, 45, 47, 49 - 55, and 61 - 63 stand rejected under 35 U.S.C. 103(a) as having been obvious over Becton Dickinson Application Note 1, in view of Maino *et al.* (FastImmune™ Assay System, 1995) and U.S. Patent No. 6,143,299.

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[20] As to claims 26 - 30, applicants do not presently traverse the denial of priority on this ground, but reserve the right to do so in a future response, should such response be required.

Applicants have previously provided evidence that the earliest date upon which Application Note 1 became public, and thus available a reference under 35 U.S.C. § 102, was December 19, 1996.

Applicants claim priority under 35 U.S.C. § 120 to U.S. patent application serial no. 08/760,447, filed December 6, 1996. As to the claims presently under examination that are entitled to the benefit of that earlier filing date — claims 19 - 21, 23 - 25, 31 - 33, 39 - 40, 43, 45, 47, 49 - 55, and 61 - 63 — Application Note 1 **is not prior art** and the rejection is in error and should be withdrawn.

As to claims 26 - 31, as to which applicants do not at present traverse the denial of priority claim, applicants file concurrently herewith the Second Declaration of John D. Altman.[21] For the reasons advanced therein, applicants respectfully submit that the Examiner's rejection is in error and should be withdrawn.

Provisional Double Patenting Rejection

Applicants acknowledge the provisional double patenting rejection over claims of copending application no. 09/526,253, and respectfully defer response until claims are held allowable in the present application.

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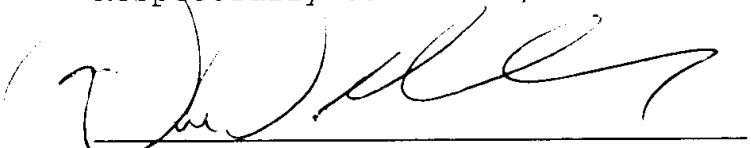
[21] Solely to expedite prosecution, and without thereby admitting to the adequacy of the Examiner's denial of priority claim, the Declaration is offered as evidence of the nonobviousness of all of applicants' pending claims.

CONCLUSION

Applicants respectfully submit that the Examiner's rejections having been fully traversed, the claims that have been withdrawn pursuant to election of species should be rejoined and all pending claims allowed.

Respectfully Submitted,



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Enclosures:

- Second Declaration of Dr. John Altman under 37 C.F.R. § 1.132, with appendices A - C

Attachments:

- Exhibits 1 - 6